Table 139.3. Delamanid drug–drug interactions with TB and HIV drugs.

Drug class	Mechanism	Impact[a]
Other tuberculosis drugs		
Rifampin	CYP 3A4 induction by rifampin	45% reduction in delamanid plasma exposure
Ethambutol		25% increase in ethambutol concentrations after 2 weeks
Isoniazid		No significant interaction
Pyrazinamide		No significant interaction
HIV antiretrovirals		
Lopinavir/ritonavir	CYP 3A4 inhibition by protease inhibitors	20% increase in delamanid exposure
Efavirenz	Weak CYP 3A4 induction by efavirenz	No significant interaction
Tenofovir		No significant interaction
QT-prolonging agents		
Fluoroquinolones, clofazimine, bedaquiline, etc.	Potential for additive QT prolongation when combined with delamanid metabolite	No observed additive QT effects, but caution advised

[a]Data from European Medicines Agency, 2013.

6a. Delamanid

CARDIAC TOXICITY

Delamanid use is associated with QT prolongation, with 3% of clinical trial patients experiencing increases in the Fredericia's corrected QT interval (QTcF) of > 60 milliseconds (ms). QT prolongation to QTcF > 500 ms occurred in 9.9 and 13.1% of delamanid-treated patients at doses of 100 and 200 mg twice daily, respectively, compared to 3.8% of patients receiving placebo, in the major phase II trial of delamanid (Gler *et al.*, 2012; Gupta *et al.*, 2015a). Increases in QT interval developed gradually over 6–10 weeks (corresponding to the time to steady state for the metabolite DM-6705, which has been shown to inhibit hERG potassium channels) and then remained stable (European Medicines Agency, 2014; Gupta *et al.*, 2015a). These observed QT prolongations have been asymptomatic, and no cases of torsades de pointes or temporally related arrhythmias have been reported (European Medicines Agency, 2014; Harausz *et al.*, 2015). Treatment-emergent palpitations were slightly more common with delamanid than with placebo, but causality is unclear (European Medicines Agency, 2014). Delamanid-associated QT prolongation does not appear to be increased with co-administration of the QT-prolonging agents levofloxacin or clofazimine in limited sample sizes (Gupta *et al.*, 2015a). Hypokalemia, hypoalbuminemia, and drug–drug interactions causing CYP 3A4 inhibition are thought to be risk factors (Harausz *et al.*, 2015).

Because of concern about QT prolongation, baseline and at least monthly EKG monitoring is recommended (with delamanid discontinuation if corrected QT exceeds 500 ms), and baseline potassium measurement and as-needed correction are also recommended. It is recommended that delamanid be avoided, except with careful risk–benefit evaluation and close monitoring, in patients with QT-prolonging conditions or medications, electrolyte disturbances, or history of or predisposing conditions for arrhythmias (European Medicines Agency, 2014), but successful use of delamanid in combination with bedaquiline for extensively drug-resistant (XDR)-TB has been reported (Lachatre *et al.*, 2016).

HEPATOTOXICITY

In a phase II extension study of delamanid, a patient who had tolerated initial treatment with delamanid 200 mg bid for 8 weeks developed drug-induced liver injury and right ventricular failure 9 days after restarting delamanid at a 100-mg bid dose. He discontinued the drug at that time but died of respiratory failure 63 days later. Four other study subjects receiving delamanid have experienced liver lab abnormalities, but all were mild and/or felt by investigators to be unrelated to the study drug (European Medicines Agency, 2013).

RISKS IN PREGNANCY

In reproductive studies in rats, delamanid was not teratogenic at up to 16 times clinical exposures, but administration of a delamanid metabolite was teratogenic at 3.6 times clinical exposures. Delamanid also caused a slight increase in the incidence of resorptions in rabbits at a maternally toxic dose of 10 mg/kg/day (European Medicines Agency, 2013).

OTHER SIDE EFFECTS

In the 8-week trial of delamanid in 321 subjects with 160 placebo controls, adverse events besides QT prolongation that were > 5% more common in the delamanid than placebo arms included nausea (38.3 vs. 33.1%), vomiting (33.0 vs. 27.5%), and headache (24.0 vs. 18.8%). These treatment-emergent adverse events were also more common in the patients randomized to the higher dose of delamanid (200